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A randomized comparative trial between Acticoat and SD-Ag in the treatment of residual burn wounds, including safety analysis

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ABSTRACT

Objective: To investigate and evaluate the clinical efficacy and safety of Acticoat with nanocrystalline silver for external use on the management of the residual wounds post-burn.

Methods: One hundred and sixty-six wounds of 98 burn patients were enrolled and divided into Acticoat group and silver sulfadiazine group in the multi-center randomized clinical trial. Acticoat was used as the treated group for those who have redness, swelling, and excessive secretion (“heavy” exudates) in the wound, Acticoat was changed once a day. When there is not much secretion in the wound, or redness and swelling were not obvious, the dressings were changed once every 3 days. Silver sulfadiazine (SD-Ag) was used as control group, which was treated under the usual clinical routine. Healing time was observed up to 20 days. Healing percentage on the 15th day after treatment was determined.

Results: Healing time was 12.42 ± 5.40 days after the application of Acticoat. This was significantly shorter than that of control wounds. The wounds of the trial group healed nearly 3.35 days earlier than the control ones. Healing percentage at 15 days in the trial wounds was 97.37%, which was higher than the control, but there was no significant difference between them. The bacterial clearance rate of the Acticoat group on the 6th and 12th day post-treatment was 16.67 and 26.67%, respectively, which was significantly higher than the control.

Conclusions: Acticoat with nanocrystalline silver promotes the healing process of residual wounds post-burn effectively. No adverse reaction of Acticoat was found during the study.

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1. Introduction

Silver dressings have a long history in use as an anti-bacterial agent. In the traditional silver formulas (with silver nitrate or silver nitrate sulfadiazine), silver ions have difficulty releasing into tissues, and the silver ions are not only combined with some components of the bacteria, but also with some components of the wound, making the anti-bacterial function of the silver ions less effective, and consequently limiting its wide use. Acticoat, made up of two layers of polyamide ester membranes covered with nanocrystalline silver ions and a core absorption layer in the middle, can successfully overcome the above-mentioned deficiencies of a silver dressing. Most importantly, the nanocrystalline silver (Acticoat) can provide lasting stable dynamic active silver for the wound, and aims therefore widely used for all kinds of wounds [1]. This study is to investigate the efficacy and safety of nanocrystalline silver (Acticoat) in the treatment of burn wounds, and to assess the clinical value of this dressing.

2. Clinical data and methods

2.1. The selection of patients

2.1.1. Standard for the selection of patients

Burn depth was assessed according to the ''Three Degrees and Four Categories Method'', and the size of the burn was determined according to the ''Role of Nine''. Residual wounds were defined as unhealed wounds 3 weeks after burn. All patients participated in the trial at their own will. In-hospital patients between 18 and 65 years old, both males and females, with no serious complications of the heart, liver, kidney, or blood system, no serious complications or serious systemic infection; diabetic patients with ulcers must control their blood sugar levels $\leq$10 mmol/L and remain at this level for over 2 weeks with no acute metabolic disorders. All patients participating in this experiment signed an informed consent acknowledging their awareness of this trial.

Altogether 111 patients were enrolled in this group, in the process of the trial, 13 patients were dropped out of the study. Among them two patients were dropped out because of silver allergy. Eight were removed because they left to their local clinic before the wound healed, therefore we do not have their related records. Three patients were dropped because of liver dysfunction. The remaining 98 patients who were included in the statistical analysis had altogether 166 residual wounds, of whom 79 patients were men and 19 women, with age of 36.81 ± 2.49 years (between 18 and 63 years old), an average post-burn time of 36.10 ± 22.51 days, and an average burn size of 54.17 ± 23.41% TBSA. For all the patients, the area covered with dressing is less than 1% TBSA.

2.1.2. Standard for exclusion of patients

Patients who were younger than 18 years old or older than 65 years old; those who had a serious disease of the heart, liver or kidney, or had a blood producing disorder, an inclination to bleed or bleeding disease; shock or serious systemic infection; pregnant or breastfeeding women; those who had an allergic reaction to silver ions, and poor adaptivity or seriously ill and cannot finish the observation period.

2.1.3. Standard for removal or dropout of patients

Patients who were found violating the requirements of the group in the process of the experiment; those who could not continue with the treatment due to certain reasons and had to terminate the experiment, or those who could not finish all the test items due to certain reasons; those who encountered unexpected events during the treatment and had to stop medication; those who annuled their agreement acknowledging their awareness of the conditions; and those who had serious complications/infections, were all removed from the trial.

2.2. Experimental method

A multi-center, randomized experimental design is adopted, with blinding and positive parallel control. The clinical trial was done in four burn centers throughout the country at the same time with the same experimental design. The observing doctor hands out the dressing to every patient according to the time that they come to the hospital and to a randomized serial number.

A nanocrystalline silver dressing (commercial name Acticoat, registration certificate number: SFDA 20043640127, made by Smith & Nephew Co. Ltd., UK, 10 cm $\times$ 10 cm/piece), was used to cover the wounds of the trial group. Silver sulfadiazine (SD-Ag, a mass fraction of 1%, approval document number: national medicine approval number: Z1202440) was used as control group. After washing and rinsing the wounds of both the treated and the control groups with sterilized distilled water, Acticoat or SD-Ag were applied to the wounds. For those who have redness, swelling, and excessive secretion (''heavy'' exudates) in the wound, the medicine is changed once a day. When there is not much secretion in the wound, and redness and swelling are not obvious, the medicine is changed once every 3 days. In the treated group, Acticoat was cut into pieces according to the size and shape of the wounds, the pieces of Acticoat were placed in distilled water till it gets wet, then covered on the wound with the blue side downward. The Acticoat was covered with an auxiliary dressing on the top. The control group was treated with 5 g SD-Ag per 80 cm^2 and changed daily. The experiment is terminated when the wounds are healed or after 20 days of medication.

2.2.1. Observation and determination of indices

The wounds were observed dynamically in the process of medication. The secretion on the wound and the condition of the swelling, pain, etc., were recorded every 3 days, assessment after the treatment was also recorded. Half of the patients in every center were selected for photographic records.

The healing percentage in the wound and the healing time were observed and recorded: the healing percentage in the wound = ((area before treatment $-$ area after treatment)/area before treatment) $\times$ 100%.

The changes of bacteria in the wounds were determined according to the result of the bacterial culture once every 6 days.

Systemic reaction and local acrimony in skin, and other side effects were observed in the whole process of the experiment.

Regular tests of blood, urine and secretions, liver and kidney function tests, and electrocardiogram tests were determined before and after the treatment.

2.2.2. Standards for efficacy assessment

Standards for the healing of wound: the wound healed was determined by inspection by two doctors. Assessment and comments on the information of every patient and the efficacy of the medicine were made.

The comparison of the healing time and healing percentage of the wound: the healing time of the wound was calculated as the number of the days for the healing of 100% of the wound. If the wound was not completely healed when the treatment period expired, the healing percentage of the wound was recorded.

Standards for the assessment of the clinical efficacy: 20 days after the application of Acticoat dressing and silver sulfadiazine, the efficacy expressed as four levels of completely healed, obviously effective, effective and ineffective were assessed. Both the healed and obviously effective levels were considered as effective, and this percentage was calculated. The criteria of the four levels of effectiveness were listed as follows:

Healed: the wound area with medicine applied on is completely healed.
Obviously effective: 70% of the wound is healed.
Effective: over 30% of the wound is healed.
Ineffective: the effective standard is not met, and the infection in the wound is not under control.

Assessment of the safety: the side effects, abnormal indices and skin allergic reactions were assessed and determined according to the five levels—clearly relevant, probably relevant, probably irrelevant, surely irrelevant, and unable to determine. The degree of side effects was described with details. The incidence of side effects was calculated.

2.2.3. Statistics

χ^2 analysis was used to compare the ordinal and cateogorical data, and *t*-test was adopted to compare the average of continuous data; Logrank test for comparing the healing time of the two groups and Wilcoxon test for comparing the healing percentage of the two group were used. Use the CMH method that takes into account the central effect to compare the comprehensive assessment of the efficacy of the two groups. Statistics and analysis of the data was performed with statistical software (SPSS).

3. Result

3.1. The healing rate and the healing time of the wound

The healing time of the residual wounds in the experimental group is shorter than that in the control group, on average 3.35 days shorter ($p < 0.01$). But the difference of healing rate in the 15 days between the two groups was not significant (Table 1).

3.2. Effective rate of the treatment of the wound

The comprehensive efficacy of the experimental group was improved from that of the control group, but the difference between the two groups in this clinical study was not significant (Table 2).

3.3. The changes of bacteria in the wound

The four centers of this clinical trial found a total of 56 bacterial strains in 166 wounds, of which 21 were *Staphylococcus aureus* (37.50%), 6 *Staphylococcus epidermidis* (10.71%), 22 *Pseudomonas aeruginosa* (39.29%), 2 *Micrococcus* (3.57%), 4 Serratieae (7.14%), and 1 *Escherichia coli* (1.79%). In the *S. aureus*, 11 were identified as MRSA, which comprised 19.64%. When the treatment of the wounds in the both groups ended, the accumulative bacterial clearance rate of the both groups was 100%. On the 6th and 12th days after the application of Acticoat, the accumulative bacterial clearing rate were 16.67 and 26.67%, respectively, which were higher than that of the control group (Table 3). For the drug resistant bacteria MRSA, the clearance rate in the 6 days was 33.33% in the Acticoat group, and 20% in the control group.

Table 1 – The healing rate and healing time of the wound in the two groups

	Number of wounds	Experiment group	Contrast group	*p*-Value
Healing rate in the 15 days (%)	83	90.76 + 14.45	88.55 + 15.64	0.508
Healing time (days)	83	12.42 + 5.40**	15.79 + 5.60	0.005

** $p < 0.01$.

Table 2 – Effective rate of the treatment of the wound in the two groups

	Number of wounds	Healed	Obviously effective	Effective	Ineffective	Total effective rate
Control group	83	76.47	17.65	5.88	0	94.12
Experiment group	83	85.29	11.76	2.94	0	97.05

Table 3 – The clearing of the bacteria in the wounds between the two groups

Bacteria category	Experiment group				Control group			
	Before treatment	6 days after treatment	12 days after treatment	After treatment	Before treatment	6 days after treatment	12 days after treatment	After treatment
Staphylococcus	11	2	2	0	10	1	2	0
MRSA	6	2	2	0	5	1	1	0
Pseudomonas aeruginosa	12	2	4	0	10	1	2	0
Micrococcus	1	0	0	0	1	0	0	0
Serratia mancescens	2	0	0	0	2	0	0	0
Staphylococcus epidermidis	3	1	1	0	3	0	1	0
Escherichia coli	1	0	1	0				
Bacterial clearing rate		16.67*	26.67*	100		11.53	19.23	
Accumulative percentage (%)								100

Notes: The data before and after treatment are the numbers of the positive bacterial strains in the bacterial test; the data of 6 and 12 days after treatment are the numbers of bacterial strains that have been cleared.
* $p < 0.05$.

3.4. *Safety assessment*

No significant differences between the two groups were found in routine blood test, and liver and renal function tests. No local allergic or systemic symptoms were found. In the 111 patients, no side effects were found relevant with the use of Acticoat.

3.5. *Typical cases*

Case 1: A 58-year-old male with 30% TBSA electrical injury, began to use Acticoat 28 days post-burn. The result of the bacterial test before treatment was MRSA, with much excretion. The wound completely healed after using Acticoat for 6 days (Photos 1 and 2).

Case 2: A 23-year-old male was burnt by alkali solution with the burn area of 73% TBSA. He began to use Acticoat 50 days post-burn. There was not much secretion in the wound before treatment, and the bacterial test was negative. After using Acticoat for 5 days, the wound was completely healed (Photos 3 and 4).

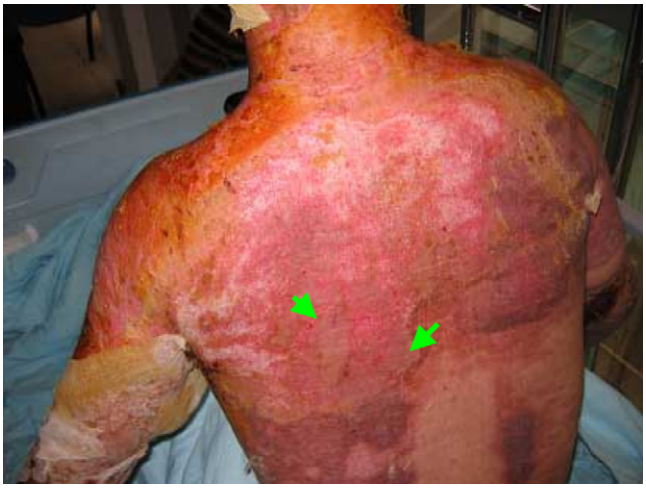

Photo 1 – Before treatment, 28 days post-burn, much excretion on the residual wounds.

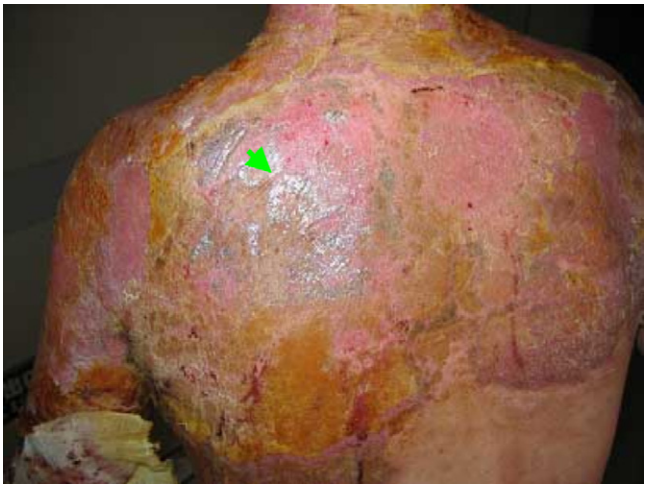

Photo 2 – Wounds completely healed after using Acticoat for 6 days.

4. Discussion

As it is well known that in the healing process of deep burn wounds, there are usually repeated blisters, and the blisters are festered and infected. This wound is called "residual wound". The termination of this condition usually takes a long time, and the treatment period can be as long as several months or even several years [2], which not only increases the workload of the medical personnel, but also brings patients huge spiritual burden and physical pain.

There are many causes for the formation of residual wounds. Firstly, when the wound with a burn depth of deep second degree heals, the secretion of the sebaceous glands remaining inside the dermis and sweat glands are blocked,

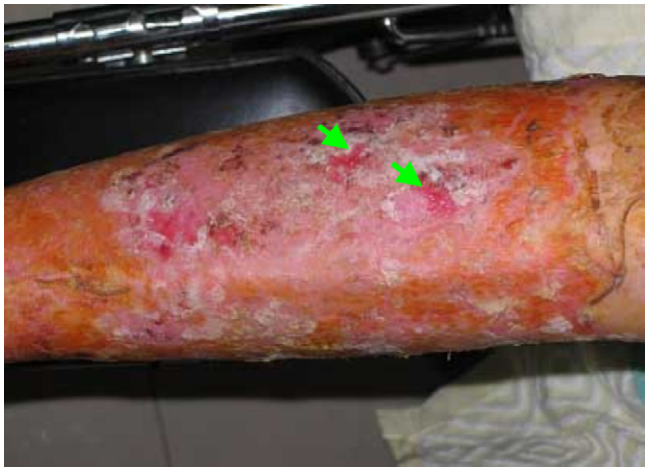

Photo 3 – Before treatment, 50 days post-burn, not much excretion on the residual wounds.

with consequent infection and festering, which is the most important reason for the formation of residual small wounds. Secondly, after the deep burn wound heals, the newly grown skin is thin, which bears pressure poorly and has a low abradability, and is prone to infection. Refractory infection may cause durable residual wounds. Infection of residual wounds is often caused by drug resistant *S. aureus* or virus [3]. The key point for the treatment of post-burn residual wounds with non-operative method is to control infections in the wound, improve cell regeneration and repair, and improve resistance of the body. Therefore, both effective antibiotic ability and enhancement of epithelium proliferation are required for an ideal topical dressing for post-burn residual wounds.

In this clinical trial, of the 166 wounds in the 98 patients from the 4 burn centers, 21 strains of *S. aureus*, 1 MRSA and 22 strains of *P. aeruginosa* were found before treatment. When the treatment was terminated, no bacteria were found in either group. But according to the bacterial tests on the 6th and 12th days after the treatment, the accumulative bacterial clearance rate in the group treated with Acticoat, was significantly higher than that in the control group. It also exhibits a powerful bacterial clearance capability on the drug resistant bacteria MRSA, which is often seen in patients with burns. As a nanocrystalline silver dressing, Acticoat displays a new state of silver—a combination of silver ion (Ag^+) and active silver (Ag^0). Whereas, the silver sulfadiazine, as a traditional therapy of silver, it is silver ions (Ag^+) that work in the solution, and the silver ions released are not only combined with some compositions of the bacteria, but also combined with the protein in blood, or deposit due to its reaction with chlorine ions, which would disable the anti-bacteria capability of silver ions. Acticoat provides the wounds a dynamic active silver with a certain concentration. In some in vitro studies, it was found that nanocrystalline silver releases silver ions faster than silver sulfadiazine, and bacteria disappear faster too [4]. In a comparison study of nanocrystalline silver, nitric silver, and silver sulfadiazine in its respective capability of killing 11 kinds of drug resistant bacteria [5], nanocrystalline silver decreased the concentration of the 11 kinds of drug resistant bacteria to a concentration below detection within 30 min. No other therapy of silver can effectively fight against 11 kinds of drug resistant bacteria within the same time as this.

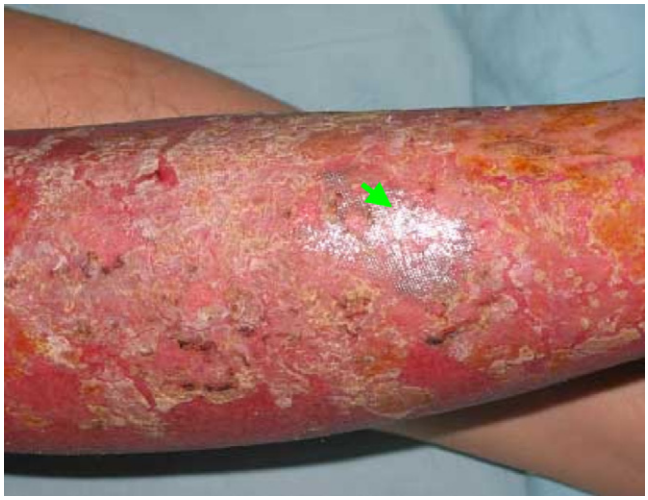

Photo 4 – The residual wounds completely healed after using Acticoat for 5 days.

In the skin grafting clinical experiment by Demling and DeSanti [6] in 20 burn patients, it was found that Acticoat can improved proliferation in the wounds. On the 7th day after the burn, the Acticoat group all healed, while in the group using antibiotics, only 55% healed. The results of our study show that Acticoat has a stronger enhancement of restoration on post-burn residual wounds. The healing time was shortened by 3.35 days compared with that in the group using silver sulfadiazine. The comprehensive effective rate is 97.05%, which was significantly higher than that in the control group. Silver sulfadiazine, which is a traditional therapy of silver, the negative ion compositions in its silver salt has some toxic effect to the tissues in the wound, which often causes prolonged healing of the wound. Nanocrystalline silver avoids this deficiency, and at the same time, it is proposed to promote apoptosis of neutral granulocytes so as to reduce the release of inflammatory mediators, thus promoting the healing of the wound.

In this study, we find that as Acticoat is easy to remove, patients have no complaint of obvious pain when changing the dressing. The secretion in the wound and swelling are obviously restrained. In the process of using Acticoat in the four centers of this experiment, no definite systemic or local side effects are found.

In summary, this study shows that Acticoat effectively improves the healing process of post-burn residual wounds, and restrains the growth of bacteria in wounds. As the application of Acticoat does not require frequent changing of the dressing, and the changing of the dressing is convenient and simple, and does not cause much pain, patients do not suffer much from the medication. It is a safer and better dressing for treatment of post-burn residual wounds.

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